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Noninvasive Breast Cancer¹

Noninvasive breast cancer comprises two distinct entities, lobular carcinoma in situ (LCIS) and ductal carcinoma in situ (DCIS). The increased use of screening mammography has caused more cases of noninvasive breast cancer to be discovered. However, the increased detection of LCIS and DCIS has posed problems in patient care for the radiologist, pathologist, surgeon, radiation oncologist, and medical oncologist. The authors review the past history of LCIS and DCIS, as well as the diagnostic challenges and therapeutic considerations for the multidisciplinary breast cancer team.

Index terms: Breast neoplasms, diagnosis, 00.32 • State-of-art reviews

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NONINVASIVE breast cancer, or carcinoma in situ, is defined as breast carcinoma limited to the ducts (ductal carcinoma in situ, or DCIS) or lobules (lobular carcinoma in situ, or LCIS) with no extension beyond the basement membrane into the surrounding stroma. The term intraductal carcinoma was originally used because of the belief that this type of cellular proliferation involved mainly the larger of the mammary ducts. It is now well established that DCIS and LCIS, as well as most benign breast proliferations, involve or arise from the peripheral portions of the branching duct system known as the terminal duct lobular unit (1). The architecture and degree of distention of the involved ductules result in different histologic patterns for the two types. However, DCIS also tends to grow along the larger ducts toward the nipple. The cells of DCIS may sometimes permeate the epidermis of the skin, resulting in Paget disease of the nipple. Prior to the advent of widespread screening mammography, noninvasive breast cancer was found at only approximately 4% of all breast biopsies (2). It commonly manifested clinically as a large mass, Paget disease, or bloody nipple discharge. All of these signs often represented an underlying extensive distribution of DCIS (3).

With the increased use of screening mammography and the improvement in mammographic technology (better screen-film systems, magnification capability, dedicated processors, etc), more cases of noninvasive breast cancer are currently being detected than ever before. The percentage of mammography-guided biopsies of occult lesions that represent DCIS today ranges as high as 20%-40% (4-7). The increased detection of carcinoma in situ poses multiple questions to the members of the multidisciplinary breast cancer team. Can the radiologist image DCIS or LCIS? Does the

imaged abnormality directly correlate with the pathologic entity of carcinoma in situ? Can the breast imager differentiate various subtypes of DCIS, some of which may be more biologically aggressive than others? Does carcinoma in situ have a different mammographic appearance than other entities such as atypical hyperplasia or invasive carcinoma?

How does the pathologist make the diagnosis of carcinoma in situ? This involves use of established criteria to differentiate carcinoma in situ from atypical hyperplasia and other benign processes. For DCIS, the pathologist is currently expected to determine the subtype(s), evaluate the margins of the tumor, and estimate its size, if possible.

For the treatment team of surgeon, medical oncologist, and radiation oncologist, the above-mentioned factors enter into the decision-making process for therapy. If the diagnosis is LCIS, can the patient be followed up closely with periodic mammography? Would the patient benefit from either unilateral or bilateral simple mastectomy? Should different subtypes of DCIS be treated differently? If the diagnosis is DCIS, should the patient undergo lumpectomy alone, lumpectomy plus radiation therapy, or mastectomy? What are the risks and benefits of these therapy options? Is there a role for adjuvant chemotherapy in the treatment of DCIS?

The purpose of this article is to attempt to discuss and answer these questions by means of a thorough analysis of carcinoma in situ.

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Abbreviations: ADH = atypical ductal hyperplasia, ALH = atypical lobular hyperplasia, DCIS = ductal carcinoma in situ, FNAC = fine-needle aspiration cytology, H-E = hematoxylin-eosin, LCIS = lobular carcinoma in situ, NSABP = National Surgical Adjuvant Breast Project.



LCIS (LOBULAR NEOPLASIA)

LCIS, also known as lobular neoplasia, was first described as a preinvasive lesion by Cornil in 1908 (8). In 1941, Foote and Stewart coined the term "lobular carcinoma in situ" (9). Even then they noted that a clinical diagnosis of LCIS could not be made and that LCIS could not be observed grossly by the pathologist but diagnosed only histologically. Around the same time, Muir used the term "intra-acinous carcinoma" for the same lesion, but this name did not come into permanent usage (10). Prior to 1980, mastectomy was the accepted treatment method for LCIS.

Currently, LCIS accounts for approximately 3%–6% of all breast malignancies (11). It is multicentric (found in more than one quadrant of the affected breast) in 70% of cases and is bilateral in approximately 30% of cases (12). It is now thought to be a marker for the risk of developing subsequent invasive carcinoma (either ductal or lobular) in either breast. This risk is approximately 25%–30% over the lifetime of a woman with the diagnosis of LCIS (13,14).

Pathologic Findings

LCIS consists of a monotonous proliferation of uniform small cells within mammary ductules of the lobule. These cells fill and distend the ductules and obliterate their lumina. The cells also grow into terminal ducts in a permeative fashion between the existing benign epithelium and the basal myoepithelium, a pattern referred to as pagetoid growth. When a limited number of terminal duct lobular units are affected by such proliferation in incomplete fashion—that is, the involved ductules have round cell proliferations of LCIS type, but they are not distended and their lumina are not completely obliterated—the term atypical lobular hyperplasia (ALH) is used. The distinction between ALH and LCIS is arbitrary and semiquantitative. The term lobular neoplasia encompasses both ALH and LCIS (14); however, it is also sometimes used interchangeably with LCIS.

A small cell type and a large cell type of LCIS are recognized. The large cell is round and has a slightly less uniform large nucleus and more abundant cytoplasm that may be eosinophilic or may contain secretory vacuoles that impart a signet-ring appearance. The two cell types often coexist, and an earlier study had sug-

gested no substantial difference between the cell types of LCIS for the subsequent risk of invasive carcinoma (12). However, one recent study has suggested that the large cell type is associated with an increased risk for subsequent invasive carcinoma (15).

Mammographic Findings

Initial studies by Snyder in 1966 and later by Hutter et al suggest that LCIS might be associated with clusters of irregular calcifications (16,17). However, recent studies by Sonnenfeld et al and Pope et al have shown that LCIS has no direct mammographic correlate (18,19). It is found incidentally by the pathologist in biopsy samples obtained for other lesions (Fig 1).

In the study of Sonnenfeld et al, 41 cases of LCIS were found. Thirty-one (76%) of the cases had incidental benign microcalcifications as the mammographic abnormality that generated the biopsy. Three (7%) of the cases were noncalcified masses, and four (10%) represented calcifications and a mass. Two (5%) of the cases had a mass with adjacent calcifications, and one case (2%) had an asymmetric opacity. LCIS was equally distributed between the left and right breast. The majority of calcifications that prompted the biopsy were found adjacent to the areas of LCIS and were associated with fibrocystic change. Rarely, when calcifications were directly correlated with LCIS, adjacent areas of benign tissue also had morphologically similar calcifications. LCIS may coexist with other entities such as sclerosing adenosis, papillomas, and radial scars (20). It may arise within a fibroadenoma, but there is no mammographic finding that suggests this association (21).

Like LCIS, its lesser counterpart ALH does not have a direct mammographic correlate. In a series of 58 cases, Helvie et al (22) found that direct mammographic-pathologic correlation could be established for 48% of cases of atypical ductal hyperplasia (ADH), but only in 9% of cases of ALH. In the few cases of ALH with direct mammographic-pathologic correlation, microcalcifications were the mammographic abnormality.

Invasive lobular carcinoma most often manifests as a spiculated mass or architectural distortion (23). These findings are not associated with LCIS. Thus, LCIS is viewed as an incidental finding in tissue from a surgical biopsy performed for another pathologic entity.

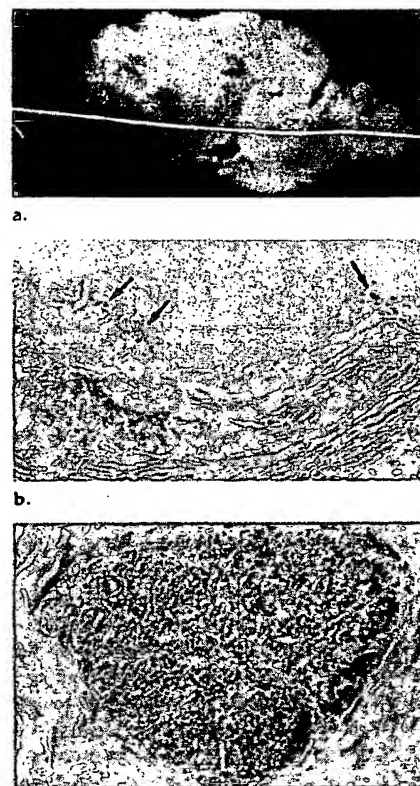


Figure 1. (a) LCIS as an incidental finding. Radiograph of specimen shows coarse, irregular calcifications (arrow). (b) At histologic study, they were seen to represent irregular calcifications within the wall of a cyst and within its degenerative contents (arrows) (hematoxylin-eosin [H-E] stain; original magnification, $\times 100$). (c) On histologic specimen, LCIS is present in a few lobules in adjacent breast tissue. Round, uniform neoplastic cells obliterate the lumina of the acini within the lobule. No calcifications are present (H-E stain; original magnification, $\times 100$).

Biologic Significance and Management

As previously noted, approximately 30% of cases of LCIS are bilateral (12). Epidemiologic data suggest that LCIS is more frequent in premenopausal women and is believed to regress in the postmenopausal state. Long-term follow-up studies have shown that the risk of redeveloping invasive carcinoma (ductal or lobular) is approximately 25%, with a lifetime relative risk 10–12 times higher than expected in the general population (12,14,15,24).

There are considerable differences in philosophy regarding the biologic significance of LCIS and its management. Earlier studies, the largest of which was performed by Haagensen

et al (11), have shown that the subsequent invasive carcinomas tended to occur after a long time interval. They also noted that the invasive carcinomas were remote from the original biopsy site, occurred equally in the ipsilateral or contralateral breast, and were often ductal rather than lobular. These findings suggested that there was probably no direct progression of LCIS to invasive carcinoma. Rather, the invasive carcinomas probably represented new lesions that may have arisen from other coexisting foci of DCIS or ADH. On the basis of these findings, Haagenson et al suggested that LCIS was only a marker lesion indicative of increased risk for future invasive carcinoma and that it should not be treated as a true malignancy (11). They introduced the term "lobular neoplasia" for this lesion. In a recent retrospective study by Page et al, however, the subsequent invasive carcinomas have been predominantly lobular. Moreover, the tendency for bilaterality was again evident (24). A short-term prospective study by Ottesen et al (15) noted that the recurrences were a spectrum of lobular and well-differentiated ductal invasive carcinoma and in the majority of cases occurred in the ipsilateral breast. Page et al believe that the results of the study of Haagenson et al reflect inclusion of a wide spectrum of lesions including a large number that would now be diagnosed as ALH.

Ipsilateral mastectomy alone in the treatment of LCIS does not eliminate the risk of invasive carcinoma, as the opposite breast is equally at risk. Non-operative observation is the more prevalent method of management for LCIS. Two deterrents for conservative management are the known association of LCIS with synchronous invasive carcinoma in about 5% of cases and the tendency for LCIS to be multicentric (12). These incidences may be even higher if labor-intensive, meticulous, pathologic sectioning techniques are employed. In a pathologic study of subcutaneous mastectomies that employed meticulous specimen mammographic-pathologic correlation (52 patients, 46 of which underwent bilateral mastectomy), Tulusan et al (25) found a 16% rate of microscopic, clinically occult invasive carcinoma that followed within 2 years of a biopsy. However, the lower incidence of invasive carcinoma in follow-up studies suggests that many of these carcinomas do not progress to clinically evident disease (26).

The role of a contralateral breast biopsy is controversial, since the like-

lihood of discovering a more significant lesion such as invasive carcinoma is slim. The presence of LCIS in the opposite breast is not likely to change the patient's risk and care considerations (26). A recent study by Ottesen et al (15) suggests that the incidence of invasive recurrences increases with the quantity and type of LCIS. Invasive recurrences were more frequent in patients with 10 or more lobules involved and in those with the large cell type of LCIS. Page et al has also noted that ALH is associated with a lower risk for subsequent invasive carcinoma in both breasts, as opposed to LCIS (two times the risk for LCIS compared to ALH) (24).

If the risk of invasive carcinoma is not acceptable to the patient and further surgical treatment is desired, bilateral simple mastectomy is a valid alternative that is consistent with the necessity to treat both breasts equally (26). Subcutaneous mastectomy may allow a considerable amount of breast tissue to remain, especially if the nipple is preserved. Low axillary lymph node dissection may also help in the detection of metastases from concurrent occult primary invasive carcinoma. To our knowledge, there is no current evidence that radiation therapy has a beneficial role in LCIS management. The potential benefit of the antiestrogen drug tamoxifen citrate for LCIS will be evaluated with the National Surgical Adjuvant Breast Project (NSABP) Breast Cancer Prevention Trial that is now under way.

Further problems regarding LCIS include the fact that LCIS is a less localized process than DCIS. The evaluation of margins in LCIS is meaningless, since LCIS is a more diffuse disease. Residual LCIS is usually present in the breast when reexcision or mastectomy is performed. Since LCIS is not a mammographically detectable lesion, there is no good way to follow up the patient for LCIS. If the subsequent invasive carcinoma is of the lobular type, it may go unrecognized mammographically in dense, premenopausal breasts, since some invasive lobular carcinomas may have a subtle, permeative growth without forming a discrete density (23). It is not only difficult to follow LCIS in dense breasts, but there is also a risk of missing a synchronous invasive carcinoma with LCIS at the time of biopsy. At our institution, each patient with LCIS is presented the facts regarding the chance of developing subsequent invasive carcinoma. These data are integrated with the patient's age and other risk factors for breast

cancer. A joint decision regarding management is then reached between the patient and her physician.

DCIS

History and Background

The first case of DCIS was illustrated in 1917 by Bloodgood (27). His proposed management for this entity included lumpectomy, radiation therapy, or both. This was not accepted by his surgical colleagues, who preferred to treat DCIS with mastectomy. This mode of therapy, with an overall cure rate of 95%–100%, continued until the late 1970s. In 1979, in Malmö, Sweden, simple mastectomy and reconstruction with implants became the recommended therapy for women with carcinoma in situ (DCIS or LCIS) up to the age of 65 years (28). In 1980, the results of a national survey by the American College of Surgeons noted that of the total of 23,972 patients with breast cancer, 1.4% had DCIS, LCIS, or both. One-half of the patients were treated for carcinoma in situ with breast-conserving therapy (biopsy alone, wide excision, or simple mastectomy), while the other half underwent either a radical, modified radical, or extended radical mastectomy. In this series, a better 5-year cure rate (83.5%) was noted in LCIS patients than in DCIS patients (68.8%) despite the fact that surgery was performed more often for DCIS. The recurrence rate was five times higher (10.5%) for DCIS compared with LCIS (2.5%) (29).

Earlier observations on the natural history of DCIS after excisional biopsy alone are based on the limited retrospective studies by Page et al and Rosen et al, which indicated a 28% risk for the subsequent development of invasive carcinoma that was usually ductal in type and occurred at or near the biopsy site (30,31). During the 1980s and early 1990s, some physicians began treating DCIS electively with excisional biopsy alone or combined with radiation therapy. Lagios et al examined patients with pure DCIS smaller than 2.5 cm in diameter. These patients all underwent lumpectomy alone, and surgical margins were free of tumor. After 4 years, however, there was a 10% rate of recurrence (32).

Currently, other biologic factors such as S-phase fraction, DNA ploidy, and hormone receptor assay are being investigated with respect to the aggressiveness of the DCIS subtypes. Clinical trials under the auspices of

the NSABP are examining various treatment modalities for DCIS. NSABP B-06 is comparing mastectomy, excisional biopsy, and irradiation versus excisional biopsy alone for DCIS. NSABP B-24 is comparing excisional biopsy with irradiation and tamoxifen citrate versus excisional biopsy, irradiation, and placebo for DCIS. Initial results of NSABP B-17, excisional biopsy alone versus excisional biopsy with irradiation, indicate breast irradiation after lumpectomy may be more appropriate than lumpectomy alone for women with localized DCIS (33).

Pathologic Findings

DCIS consists of a malignant intra-ductal epithelial proliferation, which manifests with a variety of histologic patterns and can be broadly divided into comedo and noncomedo types based on the presence or absence of comedo necrosis.

Comedo DCIS

DCIS with comedo necrosis was the common form DCIS in the pre-mammography era. It often manifested as a symptomatic lesion with nipple discharge or as a palpable mass. While most cases of DCIS are not apparent at gross pathologic examination, some of the larger lesions with comedo necrosis may appear as ill-defined, firm masses with a yellow speckled cut surface from which soft cores of necrotic material can be expressed (20). The term comedo carcinoma was coined by Bloodgood and refers to the pluglike appearance of the necrotic material that was expressed from the ducts involved with DCIS. The palpable mass associated with some cases of DCIS may be due to prominent periductal fibrosis. Microscopically, classic comedo DCIS consists of a high nuclear grade, solid intra-ductal proliferation of cells, and prominent necrosis (Fig 2). Necrosis can also be seen with a cribriform histologic pattern, which has a high or intermediate nuclear grade. The necrosis may involve the majority of the ducts containing DCIS, or, more frequently, there is a mixed pattern of necrotic and nonnecrotic areas. Calcifications are frequent and are associated mainly with the necrotic debris in the lumen of the duct.

Noncomedo DCIS

In the past few decades, a second, more subtle form of DCIS has

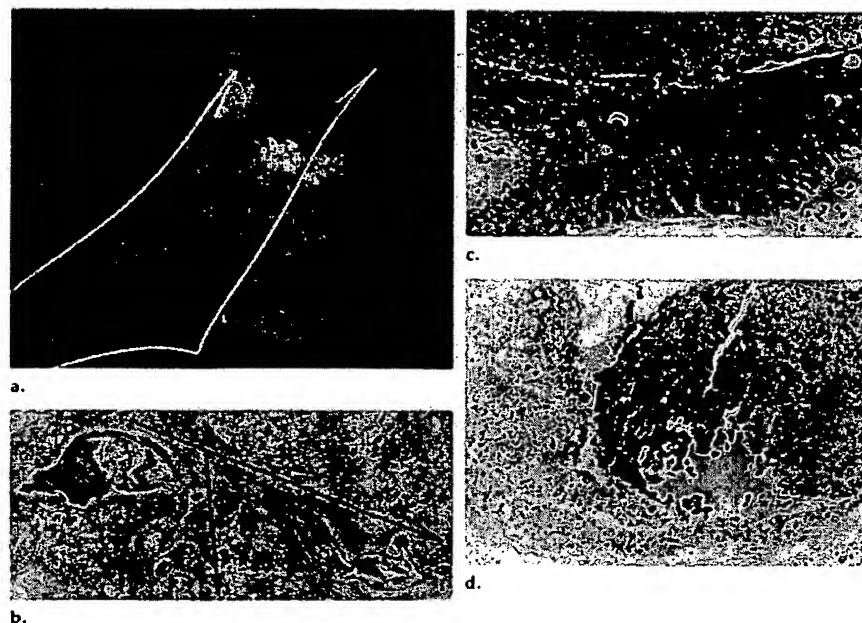


Figure 2. Comedo DCIS. (a) Radiograph of specimen shows two clusters of irregular, heterogeneous calcifications. (b) On histologic specimen, a branching duct is distended by comedo DCIS (arrows), displaying prominent necrosis. The arrows indicate the course of the duct and its branch (H-E stain; original magnification, $\times 7.5$). (c) Higher magnification shows detail of the malignant cells with a solid growth pattern and high-grade anaplastic-appearing nuclei. Amorphous, necrotic cellular debris is present at the top of the image (H-E stain; original magnification, $\times 150$). (d) A calcium stain highlights the granular calcium (stained black) within the necrotic material that accounts for the mammographic calcifications associated with comedo DCIS (von Kossa stain; original magnification, $\times 100$).

emerged. This form of DCIS consists of a low-nuclear-grade neoplastic proliferation with a deceptively bland and regular appearance of cells without obvious necrosis. This is currently referred to as noncomedo DCIS. This neoplastic proliferation can have cribriform, micropapillary, papillary, or solid patterns, which often coexist and do not represent clearly definable subtypes (Fig 3). Calcifications are frequently present. Intracystic papillary carcinoma is a special variant of noncomedo DCIS, which is histologically and biologically a low-grade lesion and often occurs in elderly women. It often manifests as a cystic mass due to marked dilatation of the involved duct. Calcifications are generally absent in this variant of DCIS (Fig 4).

Calcifications

Both comedo and noncomedo forms of DCIS are associated with calcifications. The calcifications associated with comedo DCIS are generally due to granular calcific debris within the necrotic material in the involved ducts. These casts of necrotic material tend to follow the ducts in a linear fashion, resulting in a coarse, linear

branching pattern of calcification that can be seen on the mammogram. The calcifications in noncomedo DCIS are often smaller, more discrete, and generally lamellated. These lamellations are seen only at histologic examination. They may be present freely within the lumen or within the luminal secretions. Clusters of these calcifications are also often seen in the sclerotic stroma around the ducts that have DCIS.

Significance of the Histologic Subtypes and Grade

Comedo DCIS has always been regarded as the more aggressive form of DCIS. The associated necrosis has implied a rapidly proliferating tumor that has exhausted its vascular supply. The high nuclear grade of the associated cells also supported this concept. An adverse prognosis associated with comedo DCIS was hard to prove in the past, since traditional mastectomy was often the treatment of choice and this therapy resulted in almost 100% cure. Some of the recent ancillary studies and results of clinical trials of breast-conserving procedures for DCIS have provided further evi-



Figure 3. Noncomedo DCIS. (a) Radiograph of specimen shows fine, irregular calcifications (arrows) over a wide area. (b) Histologic analysis of the biopsy specimen revealed DCIS with a cribriform pattern. The malignant cells have round, relatively regular low-grade nuclei. Irregular lamellated calcifications are present within some cribriform spaces (H-E stain; original magnification, $\times 120$). (c) Micropapillary growth pattern (arrows) is prominent in another field from the same case (H-E stain; original magnification, $\times 120$).

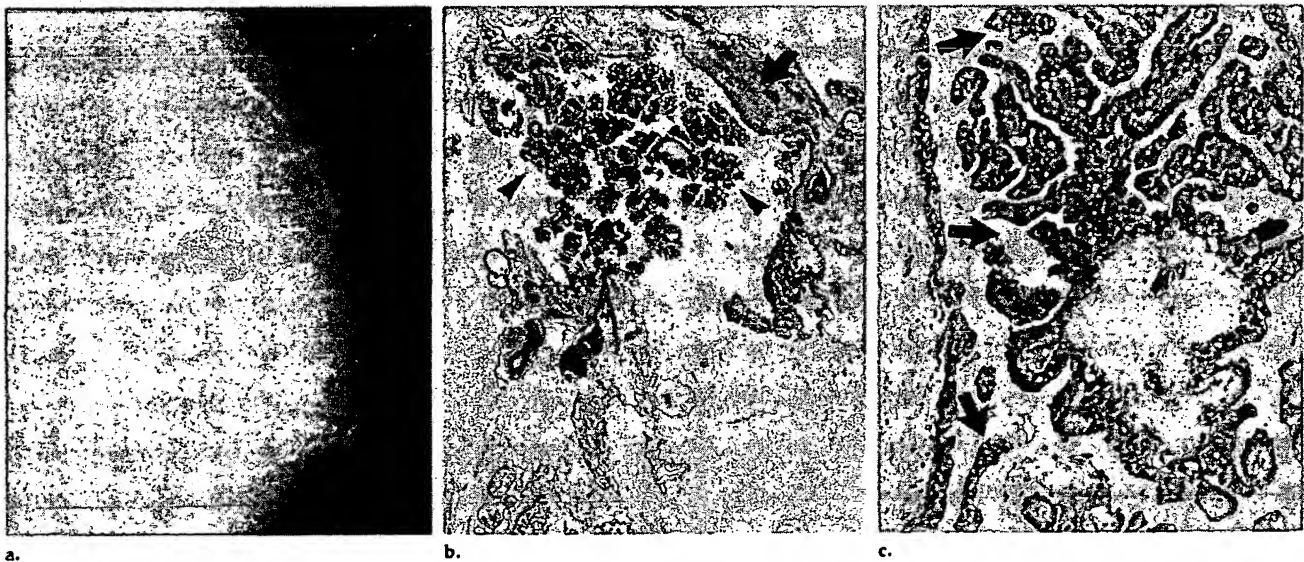


Figure 4. DCIS, atypical manifestation: intracystic papillary carcinoma (papillary DCIS). (a) A partially circumscribed, partially indistinct mass is seen on the mammogram of a 78-year-old woman. (b) At histologic study, the lesion is grossly cystic and consists of a low-grade papillary growth (arrowheads) into a cystic space, which represents a cystically dilated duct (H-E stain; original magnification, $\times 15$). Arrow = cyst wall. (c) Higher magnification shows simple papillary structures with fibrovascular cores that are lined by round or cuboid cells. These cells have stratified, slightly hyperchromatic nuclei. The cells pile up into micropapillary tufts and form somewhat rigid trabecular patterns (arrows) (H-E stain; original magnification, $\times 100$).

dence to support the more aggressive proliferative activity and anaplasia of the cells in comedo DCIS. Studies have shown that the high nuclear grade in comedo DCIS is frequently associated with aneuploidy, estrogen- and progesterone-receptor negativity, overexpression of c-erb B-2 oncogene product, and P53 suppressor gene mutation (34,35). These features are similar to those seen in poorly differentiated, high-grade invasive carcinomas. Recurrences following local excision alone or local excision and irradiation have been observed more frequently in association with comedo DCIS, high nuclear grade, or both (32,36–38). It is noteworthy that in the

study of Lagios et al (32), almost all of the recurrences were associated with high-nuclear-grade types I and II (comedo and cribriform with necrosis), which correspond to the comedo DCIS in the commonly practiced simple classification scheme described. Only one recurrence was associated with intermediate- to low-nuclear-grade types III and IV, which correspond to the common noncomedo type of DCIS. Other classification schemes that have been used by other authors are not well accepted because DCIS has too many overlapping and mixed histologic patterns to allow further subclassification in a meaningful or reproducible manner.

Problems with Microinvasion and the Role of Frozen Section

Although this article deals with noninvasive carcinoma, a comment on microinvasion is in order. By definition, DCIS and LCIS are tumors confined by the basement membrane. The determination of invasion itself is not always easy for the pathologist. Ducts cut in different planes of section may give the appearance of having tumor cells in the stroma, when in fact, the cells are still confined to the duct system. Similarly, extension of DCIS in the lobules may also simulate invasion. However, small foci of invasion may be seen microscopically in

association with DCIS without mammographic or clinical evidence of a mass. Such foci of invasion are often referred to as microinvasive if they are smaller than 2–3 mm, although currently, there is no universally accepted criterion of size for microinvasion. These foci are histologically identical to invasive ductal carcinoma, and more than one focus of invasion may be seen within the same biopsy specimen. These foci of microinvasion may be missed during pathologic evaluation because of inherent limitations with the pathologic technique. This, plus incomplete sampling of a small invasive cancer, may account for the small number of patients with DCIS who also have axillary lymph node metastases. If there is any possibility invasion has occurred, all of the tissue should be properly prepared and analyzed, even that which would have been used for hormone-receptor analysis (20).

Proper distinctions between ADH and DCIS, as well as between DCIS and invasive carcinoma, are vital in management. Whenever possible, therefore, frozen-section diagnosis should be discouraged. An optimally prepared permanent section is required to make an accurate diagnosis. For this reason, all of the biopsy tissue of a nonpalpable, mammographically localized lesion, which potentially harbors DCIS and microinvasion, should be properly prepared and analyzed (20). Histologic examination need not be compromised by removing tissue for hormone-receptor studies. If microscopic invasive carcinoma is identified, these studies can now be performed immunohistochemically on formalin-fixed, paraffin-embedded tissue used for routine histologic analysis.

Mammographic Findings

DCIS currently accounts for approximately 20% of all nonpalpable mammographically detected breast cancers (39,40). It most often manifests as one or more clusters of irregularly shaped calcifications. In a series of 100 consecutive cases of clinically occult DCIS, Stomper et al (41) noted that 72 manifested as calcifications, 10 as soft-tissue abnormalities, and 12 as both calcifications and soft-tissue masses, and six were found by the pathologist as an incidental finding. Seventy-five of the lesions were smaller than 2 cm, and 22 were smaller than 5 mm. Compared with women older than 50 years, women younger than 50 years with DCIS

were more likely to have breast calcifications and less likely to have soft-tissue masses.

The size of the DCIS is important with respect to multicentricity and occult invasion. In the series of Lagios et al (42), four of 29 (14%) lesions smaller than 25 mm were multicentric and none had foci of occult invasion; of DCIS lesions larger than 5 cm, 13 of 13 (100%) were multicentric and nine of 13 (69%) had foci of occult invasion. Similarly, Dershaw et al noted in their series of 54 cases of DCIS that all 22 cases of lesions larger than 25 mm were associated with multicentric disease (43).

The calcifications in DCIS are typically either branching, irregular, pleomorphic casts of the ducts or more focal, irregular, granular-type deposits. The calcifications may be located within debris in the ducts or within the ductal epithelium itself. It would be nice to be able to differentiate the various pathologic subtypes of DCIS according to their mammographic appearance. Stomper and Connolly analyzed 66 consecutive cases of DCIS or DCIS with small invasive foci that appeared on mammograms with microcalcifications (44). They noted that the comedo subtype was more likely to be associated with linear calcifications than the noncomedo subtypes, and noncomedo subtypes were more likely to be associated with the granular calcifications. They noted, however, considerable overlap between the two subgroups and concluded that one could not accurately predict the histologic subtype on the basis of the mammographic appearance of the calcifications.

Although DCIS most often manifests as calcifications on mammograms, other less common manifestations are also seen. Ikeda and Andersson (45) examined atypical forms of DCIS. In their series of 190 patients, 73 women did not have microcalcifications associated with DCIS. Of these, 30 had negative mammograms, 15 had circumscribed masses, and 12 had various nodular patterns. Seven of the 15 circumscribed masses represented intracystic papillary carcinoma, a subtype of DCIS. Other patients had asymmetry ($n = 1$), dilated retroareolar ducts ($n = 2$), an ill-defined mass ($n = 2$), focal architectural distortion ($n = 4$), a subareolar mass ($n = 3$), and a developing density ($n = 4$).

The question also arises of whether one can differentiate DCIS from infiltrating carcinoma at mammography. Hermann et al (45) examined 193 con-

secutive women with nonpalpable breast carcinoma: 102 had DCIS, and 91 had infiltrating carcinoma. Of the 112 women (58%) with microcalcifications, 84 (75%) had DCIS and 28 (25%) had infiltrating carcinoma. Of the 69 (36%) with a mass, 60 (87%) had infiltrating carcinoma. Of the 12 (6%) with microcalcifications and a mass, nine (75%) had infiltrating carcinoma. Thus, calcifications were more likely to be associated with DCIS. Masses, with or without calcifications, were more likely to represent infiltrating carcinoma. However, overlap existed between the two groups, and one could not rely on the mammographic findings to distinguish DCIS from small, infiltrating ductal carcinomas.

Another point relevant to the radiologist relates to the radiography of the specimen and radiation therapy. A specimen radiograph is vital in determining whether the lesion has been excised in toto. Since the majority of cases of DCIS are associated with microcalcifications, one can advocate obtaining magnification views of the specimen to ensure that all of the calcifications have been removed. When one measures mammographically the amount of tissue involved with calcifications of the comedo type, this correlates well with the area of involvement seen histologically. For noncomedo DCIS, however, the extent of the DCIS is often underestimated on the mammograms. This may be due to the fact that the calcifications at the periphery of the noncomedo DCIS subtypes are lower in density than their comedo counterpart. It is also important for the radiologist to pinpoint the location of all lesions in the specimen. We routinely insert a sterile hypodermic needle into the excised tissue at the site of the calcifications. We then submit the tissue with the needle still in place, accompanied by a copy of the specimen radiograph to the pathologist. This allows the pathologist to map out the configuration and size of the lesion and to correlate the microscopic findings with the sampled abnormality. In addition, since the radiation therapist would like to be certain that all preexisting tumor has been excised at the biopsy site, pre-radiation therapy magnification radiographs of the biopsy site are obtained in cases of DCIS that manifest with calcifications. This technique helps ensure that no residual or new calcifications are found. Postbiopsy magnification imaging is often followed with mammography every 6

months for the 1st year and annually thereafter (47).

Stereotaxic-guided needle-core biopsy and fine-needle aspiration cytology (FNAC) have been advocated for nonpalpable breast lesions. The radiologist should be aware of several facts related to these modalities. FNAC cannot allow differentiation of DCIS from invasive ductal carcinoma, whereas needle-core biopsy can. Some surgeons will perform a wide excision and axillary lymph node dissection if the cytology results are positive for adenocarcinoma and if the mammographic abnormality is suggestive of invasive carcinoma. For a mammographic abnormality suggestive of DCIS, such as a cluster of irregular calcifications, a positive FNAC result will necessitate a wide excision of the lesion. If no foci of microinvasive tumor are found, no axillary lymph node dissection is required.

If the needle-core biopsy diagnosis is DCIS, the surgeon still does not know if there is an invasive component to the tumor that has not been sampled. Parker (48) advocates treating a needle-core biopsy diagnosis of DCIS in the same fashion as an open surgical biopsy diagnosis of DCIS without clear margins. The surgeon would then perform a wide-excision lumpectomy to obtain tumor-free margins and allow the pathologist to determine if an invasive component was present in the lesion (48).

Both FNAC and core biopsy remain to be proved as accurate for small lesions, such as clustered calcifications, because of the potential for sampling errors with both modalities. Therefore, a suspicious mammographic finding still necessitates additional work-up (repeat FNAC, repeat needle-core biopsy, or surgical biopsy) if the FNAC or needle-core biopsy results are negative.

Management

Traditionally, DCIS has been treated with mastectomy (simple or modified radical), and the cure rate has been almost 100%. Lymph node metastases may be identified in 1%–2% of patients with DCIS. This is likely due to a microscopic focus of invasive carcinoma not initially identified at microscopic examination. However, routine axillary lymph node dissection is probably not necessary, since the incidence of nodal metastases is very low (49).

With the emphasis on breast-preserving therapy for invasive breast carcinoma, there is a distinct trend toward managing DCIS in a similar

conservative fashion. It may not be appropriate, however, to manage all forms and sizes of DCIS in the same fashion. In addition, concerns about multicentricity, occult invasion, and axillary metastases pose problems to the treatment team. Multicentricity represents more than one focus of DCIS within different quadrants of the breast. Multifocality refers to more than one focus within the same quadrant of the breast. The prevalence of multicentricity with DCIS has been reported to be as high as 60% (50). However, the methods of sampling the tissue varied, as did the interpretations for multicentricity. The study of Holland et al, which used Egan's technique of obtaining multiple serial subgross sections under mammographic guidance, found that true multicentric disease was very rare (50,51). In serial sections, no intervening areas of normal tissue were found. What other pathologists called multicentric disease actually may represent contiguous spread of DCIS throughout the involved duct system. Thus, one is not surprised that when DCIS recurs, more often than not it does so at or near the original biopsy site. More important, while a patient with DCIS who is treated with mastectomy has, in effect, been cured, a patient treated with conservative therapy who develops an invasive recurrence has altered her prognosis from stage 0 with almost no metastatic potential to stage I or more invasive carcinoma with metastatic potential and possibly a reduced life expectancy.

Recent attention to the morphologic heterogeneity of DCIS has led to the recognition of variations in the biologic potential among DCIS subtypes (52,53). Also, the size or extent of DCIS varies widely from a 3-mm incidental mammographically occult DCIS to very extensive *in situ* carcinoma involving several quadrants of the breast. Therefore, it is becoming obvious that one cannot apply a standard treatment for all types and sizes of DCIS to all patients. The treatment may now be individualized based on the subtype or grade of DCIS and its estimated size in an effort to obtain optimal results. Multicentric foci, if present, are of little biologic significance, since the recurrences almost always are found at or near the biopsy site; they are very rare elsewhere in the breast (36,53).

The recent reviews of DCIS cases treated with conservative therapy indicate that there is a 12.3%–43.1% recurrence rate with local excision alone (53–55). The recurrence rate is

2%–17% when radiation therapy is added (36,56–58). The long-term ablative effects of radiation therapy for DCIS remain to be seen. Some of the recent results with and without radiation therapy are summarized in Tables 1 and 2. The recurrences have tended to be equally divided between DCIS and invasive carcinoma. It is noteworthy that most recurrences, when noted, have been associated with comedo DCIS or high-nuclear-grade DCIS. The variation in recurrence rates in different studies reflects differences not only in study design but also in the inclusion of somewhat heterogeneous groups of DCIS (both by extent and morphology). When a decision for conservative management is made, the patient should be fully aware of the risk of future invasive carcinoma, as well as the necessity of lifelong surveillance.

ADH

It is appropriate to include ADH in the discussion of the DCIS because they are related lesions. As has been previously mentioned, DCIS can manifest as either a high-grade comedo or low-grade noncomedo form. A low-grade intraductal proliferation with partial or incompletely developed features of noncomedo DCIS is referred to as ADH. It is not surprising that ADH also frequently manifests with calcifications (22). ADH is currently associated with an increased relative risk for future invasive carcinoma. This risk is approximately five times that of the referenced population. This risk is about half that associated with DCIS if no further treatment is given, but the risk is doubled if there is a first-degree relative with breast cancer (59). Just as ALH and LCIS together are considered to be lobular neoplasia, low-grade DCIS and ADH may be regarded as lesions in the ductal neoplasia spectrum. At this time, the management for ADH is close observation with regular clinical and mammographic examinations.

CONCLUSION

Both LCIS and DCIS represent lesions that are limited to the duct system and have no metastatic potential. Currently, the diagnosis of LCIS serves as a warning to the patient that invasive breast cancer has a one in four to one in three chance of occurring during her lifetime. Management decisions, often bilateral simple mastectomy or excisional biopsy with close clinical and mammographic fol-

low-up after biopsy alone, must be tailored to the patient.

DCIS represents a more heterogeneous morphologic spectrum with probably varied biologic propensities. It is likely that not all forms of DCIS progress to invasive ductal carcinoma. Moreover, those that do progress may not do so at the same rate. DCIS with comedo necrosis is viewed as more aggressive than the noncomedo subtypes and potentially is the subtype that would benefit from adjuvant therapy or traditional mastectomy depending on the extent of disease and the age of the patient. Noncomedo DCIS might be managed more conservatively.

It is somewhat ironic that a potential "good news" lesion for the patient such as DCIS may have more confusion surrounding its management than does its invasive counterpart. Certainly, if one has to have cancer, one would prefer that it not be invasive. However, the decision of whether to undergo excisional biopsy alone, excisional biopsy and irradiation, or mastectomy may not be clear-cut. Further studies are needed to understand better the natural history of DCIS, as well as the biology of its subtypes. Perhaps then the management of this entity will be clearer for both patient and physician. ■

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Table 1
DCIS: Local Excision and Observation (Prospective Studies)

Reference	No. of Patients	Median Follow-up (mo)	Total No. of Recurrences*	No. of Recurrences of DCIS, Invasive Carcinoma	Comments
Fisher et al, 1993 (33)	391	43	64 (16.4)	32, 32	Margins negative; 42.2% < 0.1 cm, 73% < 1.0 cm, 88% < 2.0 cm
Fisher et al, 1991 (36)	21	39	9 (43.0)	4, 5	Only a small number with small tumors
Lagios et al, 1990 (53)	79	68	10 (12.6)	5, 5	Mammographically detected lesions ≤ 2.0 cm at pathologic-mammographic correlation; recurrences mainly with comedo and high nuclear grade
Schwartz et al, 1992 (37)	72	47	11 (15.3)	8, 3	Subclinical only†, < 2.5 cm area of calcifications on mammogram; focal positive margin accepted; all but 1 recurrence with comedo DCIS
Ottesen et al, 1992 (60)	112	53	24 (22)	19, 5	Size < 5 mm to > 4.0 cm; status of margins known only in a few cases; 70% recurrence at site of original lesion, significantly more with larger size, comedo necrosis, and intermediate to large cell types

* Numbers in parentheses are percentages.

† Subclinical: cases without mass, discharge, or Paget disease.

Table 2
DCIS: Local Excision and Radiation Therapy

Reference	No. of Patients	Size* (cm)	Median Follow-up (mo)	Total No. of Recurrences†	No. of Recurrences of DCIS, Invasive Carcinoma	Comments
Fisher et al, 1993 (33)	399	NA	43 (mean)	28 (7.0)	20, 8	Negative margins; 44.6% < 0.1 cm, 74.4% < 1.0 cm; 87.7% < 2.0 cm; no comment on relation of recurrences to DCIS subtype and size
Fisher et al, 1991 (36)	27	2.2	83	2 (7)	1, 1	Comedo necrosis and nuclear grade related to recurrence; negative margins
Silverstein, 1991 (57)	104	≤ 4	51	7 (7)	5, 2	Six of 7 recurrences with comedo DCIS; negative margins
Solin et al, 1991 (58)	261	NA	78	28 (16)	14, 14	Subclinical only; histologic subtypes unknown; margins evaluated only in some cases
Bornstein et al, 1991 (56)	38	NA	81	8 (2)	3, 5	Microscopic margins not evaluated

* NA = not available.

† Numbers in parentheses are percentages.

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